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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/256,237	02/24/99	HEIDTMANN H	026083/0195

HM22/0831

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EXAMINER	
DAVIS,M	
ART UNIT	**PAPER NUMBER**
1642	8

DATE MAILED: 08/31/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/256,237	
Examiner	**Group Art Unit**
M. T DAVIS	1642

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 (MONTH(S)) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 7-14-00.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 19, 21, 23, 25 is/are pending in the application.

Of the above claim(s) 19 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 21, 23, 25 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 8

☐ Interview Summary, PTO-413

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

Applicant's election with traverse of group II, claims 21, 23, and 25 in Paper No. 6 is acknowledged. The traversal is on the ground(s) that group III, claim 19 should be joined to group II upon allowance of the claims of group II under the In re Ochiai guidelines. This is not found persuasive because the scope of group III is different than that of group.II.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 21, 23, and 25 are examined.

PRIORITY DATE

The Examiner has established a priority date (01/16/98) for the instantly claimed application serial number 09/256237 as the application 197 01 141.1 to which priority is claimed is not available. Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 21, 23 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21, 23 and 25 are indefinite because claim 25 recites the language "bound' to. It is not clear how component (d) is bound to component (b). Is it per antibody/antigen type of binding or by a peptide bond?

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 21, 23 and 25 are rejected under 35 U.S.C. 112, first paragraph.

Claims 21, 23, and 25 are drawn to a polypeptide encoded by a nucleic acid construct comprising; a) at least one promoter, linked to b) at least one nucleic acid sequence which encodes an endogenous active compound, which is linked to c) at least one nucleic acid sequence which encodes an amino acid sequence cleavable specifically by an enzyme, which is released from a mammalian cell, and which is linked to d) at least one DNA sequence which encodes a

polypeptide which is bound to said active compound via said cleavable amino acid sequence, and inhibits the activity of said active compound, and wherein said nucleic acid component c) does not naturally occur as linking to said nucleic acid sequence b) to said nucleic acid d). Claims 21, 23, and 25 are also drawn to a method of making the claimed polypeptide.

The specification discloses the use of the claimed polypeptides for treating diseases which have an increased local formation of prosteases such as tumors, allergies, autoimmune diseases, infections, inflammations, transplant rejection reactions, thrombosis and blood vessel occlusions, and tissue injuries, including injuries to the central nervous system and damage to the nervous system.

The specification discloses in a prophetic example a preparation of a nucleic acid construct encoding factor X (component b) , wherein its natural cleavage site is replaced by a nucleotide sequence encoding a prostate specific antigen (PSA)-specific cleavage site (component c). The specification further discloses that component d) is a naturally occurring precursor of factor X (p.43). The specification also discloses that factor X, when cleaved at its natural cleavage site, will result in coagulation active factor Xa. The specification further discloses that the claimed polypeptide could be used to treat prostate carcinoma metastases, wherein the prostate carcinoma metastases secrete PSA, which is an enzyme, and wherein the prostate carcinoma metastases induces angiogenesis, i.e. growth of new blood vessels.

It is questionable that the claimed polypeptide could be used for treating tumors in a patient with prostate cancer. An anti-tumor agent must accomplish several tasks to be effective.

It must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. For example, it is well known in the art that most PSA in the serum is inactive, by complexing with a protease inhibitor, ACT, and that although the secreted PSA at the extracellular site of tumor cells is initially active, it could readily form complexes with ACT (Denmeade, SR et al, 1997, Cancer Res, 57(21): 4924-3, especially p. 4949). Thus, it is questionable whether there is adequate amount of active PSA to cleave the claimed polyppetide at the site of metastasis, whether there is adequate contact between the claimed polypeptide and PSA for sufficient period of time, and adequate amount of activated factor X at the site of tumor.

. Furthermore, as drawn to factor X, it is not clear what compound is the precursor of factor X. It is not clear how the precursor of factor X is bound to factor X via a PSA-specific cleavage site, i.e. by what type of bondage, and by which site of factor X the precursor interacts with factor X and inhibits the activity of factor X. It is not clear whether the presence of the precursor, which is presumably a large molecule, and is bound to the PSA-specific cleavage site, a small peptide, would interfere with the activity of PSA in cleaving the PSA-specific cleavage site. It is not clear how and what would trigger the precursor of factor X to be released from factor X, and the inhibition of factor X by its precursor is abolished at the site of tumor. Even if there is adequate amount of activated factor X, i.e. factor Xa, at the site of tumor to induce blood coagulation, it is questionable whether there is adequate blood coagulation to inhibit growth of new blood vessels induced by prostate cancer metastasis, and inhibit prostate cancer metastasis. In

addition the target cells must not have alternate means of survival despite action at the proper site of the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieveing successful therapy. The polypeptide may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the protein. In addition, the polypeptide may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues wherer the peptide has no effect, circulation into the target area may be insufficient to carry the polypeptide and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to theses issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which woul allow one of skill in the art to predict the efficacy of the claimed polypeptide for treating prostate cancer metastasis with a reasonable expectation of success.

It is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in

the art would accept the assertion that the claimed polypeptide could be used for treating prostate cancer metastasis. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed polypeptide could be used for treating prostate cancer metastasis. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages

1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2). The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed polypeptide for treating prostate cancer metastasis with a reasonable expectation of success.

In view of the above, undue experimentation would be required to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

In the event that Applicant could overcome the above 101 and 112, first paragraph rejection, claims 21, 23 and 25 are still rejected under 112, first paragraph, scope.

Claims 21, 23 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide encoded by a nucleic acid construct comprising; a) at least one promoter, linked to b) at least one nucleic acid sequence which encodes an endogenous active compound, which is linked to c) at least one nucleic acid sequence which encodes an amino acid sequence cleavable specifically by an enzyme, which is released from a target tumor cell, and which is linked to d) at least one DNA sequence which encodes a polypeptide which is bound to said active compound via said cleavable amino acid sequence, and inhibits the activity of said active compound, does not reasonably provide enablement for a

polypeptide encoded by a nucleic acid construct comprising; a) at least one promoter, linked to b) at least one nucleic acid sequence which encodes an endogenous active compound, which is linked to c) at least one nucleic acid sequence which encodes an amino acid sequence cleavable specifically by any enzyme, which is released from any mammalian cell, and which is linked to d) at least one DNA sequence which encodes a polypeptide which is bound to said active compound via said cleavable amino acid sequence, and inhibits the activity of said active compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 21, 23, and 25 are drawn to a polypeptide encoded by a nucleic acid construct comprising; a) at least one promoter, linked to b) at least one nucleic acid sequence which encodes an endogenous active compound, which is linked to c) at least one nucleic acid sequence which encodes an amino acid sequence cleavable specifically by an enzyme, which is released from a mammalian cell, and which is linked to d) at least one DNA sequence which encodes a polypeptide which is bound to said active compound via said cleavable amino acid sequence, and inhibits the activity of said active compound, and wherein said nucleic acid component c) does not naturally occur as linking to said nucleic acid sequence b) to said nucleic acid d). Claims 21, 23, and 25 are also drawn to a method of making the claimed polypeptide.

Claims 21, 23 and 25 read on a polypeptide encoded by a nucleic acid construct comprising; a) at least one promoter, linked to b) at least one nucleic acid sequence which encodes an endogenous active compound, which is linked to c) at least one nucleic acid sequence

which encodes an amino acid sequence cleavable specifically by any enzyme, e.g. any serum proteases, such as trypsin, chymotrypsin, etc.. which is released from any mammalian cell, including normal cell, and which is linked to d) at least one DNA sequence which encodes a polypeptide which is bound to said active compound via said cleavable amino acid sequence, and inhibits the activity of said active compound, and wherein said nucleic acid component c) does not naturally occur as linking to said nucleic acid sequence b) to said nucleic acid d).

It is unpredictable that the claimed polypeptide, wherein the component c) is a nucleic acid sequence which encodes an amino acid sequence cleavable specifically by any enzyme, e.g. any serum proteases, such as trypsin, chymotrypsin, etc.. which is released from any mammalian cell, including normal cell, would be stable in serum or blood or extracellular fluid before reaching the target cells. It is well known in the art that several proteases exist in the serum (Denmeade SR et al, 1997, *supra*, p.4926). Thus the claimed polypeptide would be cleaved in the serum or blood before reaching the target cells, and the action of the actived compound b) in the circulation would be undesirable, e.g. blood coagulation.

In view of the above, it would be undue experimentation to one of skill in the art to use the claimed polypeptide as broadly as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The

examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

August 16, 2000

SUSAN UNGAR, PH.D
PRIMARY EXAMINER